Interaction Study between Digoxin and a Preparation of Hawthorn (*Crataegus oxyacantha*)

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Hawthorn, an herbal supplement, is currently being evaluated for the treatment of heart failure. The flavonoid components of hawthorn may be responsible for hawthorn's beneficial effects in the treatment of heart failure. However, these components may also affect P-glycoprotein function and cause interactions with drugs that are P-glycoprotein substrates, such as digoxin, which is also used to treat heart failure. Therefore, the purpose of this study was to determine the effect of hawthorn on digoxin pharmacokinetic parameters. A randomized, crossover trial with 8 healthy volunteers was performed evaluating digoxin 0.25 mg alone (D) for 10 days and digoxin 0.25 mg with Crataegus *special extract WS 1442 (hawthorn leaves with flowers; Dr. Willmar Schwabe Pharmaceuticals) 450 mg twice daily (D + H) for 21 days. Pharmacokinetic studies were performed for 72 hours. There were no statistically significant differences in any measured pharmacokinetic parameters. The* $AUC_{0-\infty}$, C_{max}-C_{min}, C_{min}, *and renal clearance for the D group were 79 ± 26 mcg•h/L, 1.4 ± 0.7 mcg/L, 0.84 ± 0.2 mcg/L, and 74 ± 10 mL/min versus 73 ± 20 mcg•h/L, 1.1 ± 0.1 mcg/L, 0.65 ± 0.2 mcg/L, and 81 ± 22 mL/min for the D + H group, respectively (*$p > 0.05$*). Following 3 weeks of concomitant therapy, hawthorn did not significantly alter the pharmacokinetic parameters for digoxin. This suggests that both hawthorn and digoxin, in the doses and dosage form studied, may be coadministered safely.*

Keywords: *Hawthorn; digoxin; pharmacokinetics; heart failure*

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Crataegus oxyacantha, an extract of the herbal supplement hawthorn, has been used to treat a number of cardiovascular ailments, including heart failure, angina pectoris, and hypertension. Studies have shown that *Crataegus* extract may have positive inotropic, vasodilatory, and antioxidative properties.[1-3] This compound also improves endothelial function.[4,5] Based in part on these effects, *Crataegus* extract (hawthorn) is currently being studied for the treatment of heart failure in a large mortality trial.[6]

Hawthorn is made up of a number of compounds, including flavonoids, which may be responsible for hawthorn's cardiovascular effects.[6] In addition, recent studies evaluating other natural compounds that contain flavonoids as well as flavonoids themselves have demonstrated alterations in P-glycoprotein activity.[7-11] This may have important consequences in regard to drugs that are P-glycoprotein substrates. Since P-glycoprotein is found in high amounts in both the gut and kidney and is an efflux transporter, change in activity can lead to alterations in the absorption and clearance of drugs that are P-glycoprotein substrates.

One drug that is a P-glycoprotein substrate is digoxin. Digoxin is indicated for the treatment of symptomatic heart failure due to systolic dysfunction.[12] If hawthorn is shown to be beneficial in the treatment of heart failure, it is likely that it will be coadministered with digoxin. A hawthorn-digoxin interaction is

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widely noted in the herbal medicine literature, but neither case reports nor pharmacokinetic/pharmacodynamic data have been reported. Since hawthorn may theoretically alter P-glycoprotein activity due to its flavonoid components, it therefore may also affect digoxin pharmacokinetic parameters. The purpose of this study was to determine if hawthorn, when coadministered with digoxin, would alter digoxin pharmacokinetic parameters. The findings from this study may have important implications regarding treatment of heart failure with hawthorn.

METHODS

A total of 8 healthy subjects completed an open-label, randomized crossover trial evaluating the effect of hawthorn on the pharmacokinetic parameters of digoxin. After approval from the human subject institutional review board and before study entry, informed consent was obtained from each subject. Inclusion criteria included the following: age > 18 years, serum creatinine < 1.2 mg/dL, and bilirubin < 1.5 mg/dL. Individuals taking concurrent scheduled medications (excluding oral contraceptives), those with significant medical histories, and smokers and pregnant females were excluded from the study. Subjects were also prohibited from taking vitamins, dietary supplementation, or herbal supplements during the study period. Grapefruit juice, grape juice, and red and white wine were also prohibited throughout the study period.

Subjects were admitted as outpatients to the General Clinical Research Center, and after physical examination and baseline laboratory measurements were obtained, patients were randomized into one of two groups: digoxin 0.25 mg daily for a 10-day period (D) or digoxin 0.25 mg daily and *Crataegus* special extract WS 1442 twice daily (one tablet contained 450 mg dry extract of hawthorn leaves with flowers standardized to 84.3 mg of oligomeric procyanidines; Dr. Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany) for a 21-day period (D + H). A 21-day period was employed for the D + H treatment group to allow for steady-state concentrations for both digoxin and hawthorn. Only a 10-day period was used for the D group since steady-state levels would be achieved by this time and would therefore decrease the exposure of healthy volunteers to digoxin. After each treatment period, there was a 21-day washout period, and subjects were then crossed over to the opposite treatment. Compliance was determined by measuring digoxin trough levels after 5 days (also used as a safety measurement) and comparison with trough digoxin levels on pharmacokinetic sampling days and by medication vial inspection. Digoxin was administered at 0900 h and hawthorn at 0900 h and 2100 h.

Pharmacokinetic data were collected during 12-hour clinic stays starting on digoxin-only day 10 and on digoxin + hawthorn day 21. Blood samples (7 mL, no anticoagulant) were drawn from each subject immediately before administration of digoxin and/or hawthorn (time 0) and then at 0.25, 0.5, 1, 1.5, 2, 4, 6, 8, and 12 hours after administration of the medications; subjects were fitted with hep-lock catheters to facilitate the repeated blood draws. Catheters were removed after the 12-hour blood draw. Subjects were required to return to the clinic for blood draws at 24, 48, and 72 hours after the initial blood draw. Urine was also collected for a 24-hour time period, beginning at the baseline blood draw for determination of digoxin renal clearance. All patients were asked to void prior to the start of the collection period. For the D + H group, hawthorn administration continued throughout the 72-hour data collection period. Pharmacodynamic measurements included blood pressure (three measurements, 5 min apart, in seated position by automated blood pressure machine; Alaris Medical Systems IVAC Vitacheck Model 4415) and a standard 12-lead electrocardiogram (for heart rate and PR interval measurements), which was obtained prior to and after each treatment phase. All patients were required to be in a seated position for at least 15 minutes prior to pharmacodynamic assessment. Subjects were questioned about side effects or adverse reactions between days 5 and 7 in the D phase and between days 8 and 10 in the D + H phase.

Digoxin Analysis

Serum and urine samples were assayed for digoxin using the kinetic interaction of microparticles in solution (KIMS) immunoassay technique on a Roche Integra analyzer. The assay has a validated test range of 0.2 to 0.5 ng/mL. Any samples with an initial concentration above 5.0 ng/mL were diluted with a zero calibrator and reanalyzed. The interassay coefficients of variation were 9.6% at 0.85 ng/mL and 3.6% at 3.45 ng/mL. To determine if hawthorn interfered with the digoxin assay, 2 subjects were administered 450 mg of hawthorn twice a day for 7 days. After 7 days, blood samples were obtained and measured for digoxin concentrations. Both samples demonstrated serum digoxin concentrations below the detectable range of the assay (< 0.2 ng/mL).

Data Analysis

Pharmacokinetic parameters were determined by noncompartmental methods and inspection of the data, when appropriate. Specifically, the area under the serum concentration-time curve (AUC) to 24 hours (AUC_{0-24}) and to the last measured time point (AUC_{0-72}) was determined by the linear trapezoidal method with extrapolation to infinity ($AUC_{0-\infty}$). The elimination half-life ($t_{1/2}$) was determined by linear regression analysis of the terminal phase of the log concentration-time profile. The minimal serum concentrations (C_{min}), maximal serum concentration (C_{max}), and time to C_{max} (t_{max}) were determined by inspection of the available data points. Renal clearance (CL_R) was calculated as the total amount of unchanged drug excreted into the urine (Ae) over 24 hours divided by the AUC_{0-24}. Statistical comparison between the two phases was performed by a paired *t*-test. A $p \leq 0.05$ was considered the critical probability level. The reported data are represented as the mean and standard deviation.

RESULTS

There were 11 subjects screened with a total of 8 patients completing the study, 4 male and 4 female. The subjects ranged in age from 19 to 43 years old (mean = 28 ± 6) with a mean weight of 69 ± 13 kg. One subject did not complete the study due to palpitations that were thought to be secondary to digoxin, and 1 patient was not able to complete the study due to a family emergency. One volunteer withdrew from the study for personal reasons before beginning the protocol. In regard to compliance, inspection of subject medication vials indicated that no doses were missed. In addition, there was no difference in digoxin trough concentrations at the mid-phase safety check and at the start of pharmacokinetic sampling (0.69 ± 0.4 mcg/L vs. 0.84 ± 0.2 mcg/L for the D group and 0.63 ± 0.1 vs. 0.65 ± 0.2 mcg/L for the D + H group, $p > 0.05$, respectively).

Mean pharmacokinetic parameters for serum concentrations of digoxin are shown in Table I, and the mean serum concentration-time profiles are displayed in Figure 1. Overall, digoxin concentrations are slightly lower in the D + H group. However, there were no statistical differences between the two groups. For C_{min}, the difference approached significance ($p = 0.054$), with 6 of 8 patients in the D + H group having lower concentrations as compared to the D group.

Overall, there were no significant differences in the pharmacodynamic parameters measured from baseline values for either group. The baseline PR interval for the D and D + H phases was 149 ± 20 msec and 150 ± 16 msec ($p > 0.05$), respectively. Following each phase, the PR interval increased to 156 ± 24 msec and 152 ± 14 msec for D and D + H, respectively. The mean change in PR interval for D and D + H was 6.5 ± 11 msec versus 1.0 ± 13 msec ($p > 0.05$), respectively. Baseline heart rate (HR) during the D and D + H phases was 65 ± 6 beats/min and 64 ± 6 beats/min ($p > 0.05$), respectively. Following each phase, the HR was 62 ± 4 and 65 ± 7 for D and D + H, respectively. The mean change in HR for D and D + H was –2.5 ± 8 beats/min and 1 ± 6 beats/min ($p > 0.05$), respectively.

The hawthorn and digoxin were well tolerated. In the digoxin-only group, 1 patient noted nausea, which

Table I Pharmacokinetic Parameters

Parameter	D	D + H	% Change
AUC_{0-24} (ng•h/mL)	23 ± 4	22 ± 4	–6
AUC_{0-72} (ng•h/mL)	49 ± 9	46 ± 11	–7
$AUC_{0-\infty}$ (ng•h/mL)	79 ± 26	73 ± 20	–8
C_{max} (ng/mL)	2.1 ± 0.6	1.8 ± 0.2	–14
C_{min} (ng/mL)	0.84 ± 0.2	0.65 ± 0.2	–23
C_{max}-C_{min} (ng/mL)	1.4 ± 0.7	1.1 ± 0.1	–17
t_{max} (h)	1.3 ± 0.5	1.0 ± 0.5	–23
$t_{1/2}$ (h)	50 ± 15	48 ± 6	–4
CL_R (mL/min)	74 ± 10	81 ± 22	+9

Results expressed as mean ± standard deviation. D, digoxin-alone group; D + H, digoxin and hawthorn group; AUC, area under the concentration-time curve; C_{max}, maximum concentration; C_{min}, minimum concentration; t_{max}, time to maximum concentration; $t_{1/2}$, half-life; CL_R, renal clearance.

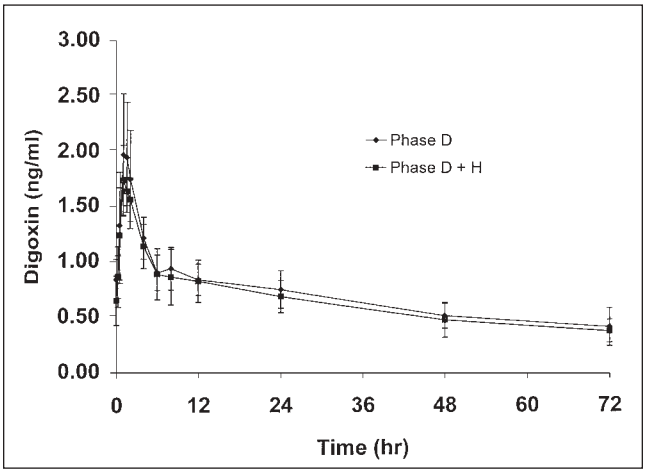

Figure 1. Mean serum concentration-time curve for digoxin. D, digoxin alone; D + H, digoxin + hawthorn.

lasted for 1 to 2 days, and in the D + H group, 2 patients complained of mild nausea, which resolved in 1 day. In the combination group, 1 subject complained of flatulence and insomnia, and 1 subject complained of headache and dizziness. These effects were mild and resolved in a day.

DISCUSSION

This study demonstrated no statistically significant difference in digoxin pharmacokinetic or pharmacodynamic parameters when coadministered with hawthorn over a 3-week time period. These findings are in contrast with those that have demonstrated significant reductions in digoxin AUC, C_{max}, and C_{min} when digoxin was given together with St. John's wort, a compound containing many of the same constituents as hawthorn.[7] These differences were at least partly attributed to induction of the P-glycoprotein transporter.[7] In particular, both are rich in various flavonols, including rutin, quercetin, isoquercitrin, and hyperoside, all of which are present in both products.[13-15] These similarities are of significance as prior publications have suggested that compounds such as rutin, quercetin, and hyperoside may be capable of altering the activity of various drug-metabolizing enzymes.[16] Even more significant in relation to effects on digoxin is the mounting evidence that quercetin, present in both St. John's wort and hawthorn, is capable of altering P-glycoprotein-mediated drug transport.[10,11,17] It could also be hypothesized that rutin and isoquercitrin, both quercetin glycosides, have similar abilities to alter P-glycoprotein activity. Erlund et al[18] demonstrated that quercetin was present in plasma following oral administration of both quercetin aglycone and rutin and that both quercetin and rutin are mainly present in the plasma as quercetin glucuronides and/or sulfates.

Despite the similarities between hawthorn and St. John's wort, important differences in their constituents may contribute to their disparate effects on digoxin pharmacokinetics. In addition to its flavonol content, hawthorn contains numerous other compounds, including chlorogenic acid, epicatechin, ursolic acid, and proticatecholic acid, none of which have been shown to alter drug metabolism or transport. Conversely, some additional compounds in St. John's wort include hyperforin, adhyperforin, and hypericin. Perloff et al[19] have shown that hypericin strongly induces P-glycoprotein in vitro and may be the principle component responsible for the P-glycoprotein induction observed with St. John's wort in vivo. Thus, it is likely that these differences explain why hawthorn did not alter digoxin pharmacokinetics to a similar extent as previous studies of St. John's wort.

These findings have important implications not only for the concomitant use of digoxin and hawthorn but also for the likely impact of hawthorn on other P-glycoprotein substrates. Digoxin is well recognized as a P-glycoprotein substrate[20] and is only minimally metabolized in humans.[21] As a result, digoxin has been widely used as a model P-glycoprotein substrate. The relatively weak effects of hawthorn on digoxin observed herein suggest that, at similar doses, hawthorn is unlikely to alter the P-glycoprotein-mediated transport of other compounds.

The lack of a pharmacokinetic interaction between hawthorn and digoxin does not, however, rule out a pharmacodynamic interaction, which is particularly concerning given their potential for use in similar patient populations. As a result, we evaluated ECG, heart rate, and blood pressure parameters and found no evidence of any such interaction. However, there is still a distinct possibility that hawthorn may increase digoxin's effect on contractility. As more is learned about the mechanism(s) by which hawthorn works in heart failure, it is becoming increasingly clear that it is unique from that of digoxin. Although, like digoxin, there is some evidence of positive inotropic effects associated with hawthorn, hawthorn is associated with a slight increase in heart rate, opposite of what would be expected with digoxin.[2] Furthermore, one of the main effects of hawthorn seems to be its ability to produce endothelium-dependent vasodilation, an effect not seen with digoxin.[2,5,22]

In the interpretation of both the pharmacokinetic and the pharmacodynamic results, particular aspects of the study design and study limitations warrant additional consideration. First, as part of the study design, hawthorn was administered simultaneously with digoxin. Coadministration in this manner allowed for inference regarding both P-glycoprotein activity and other factors, such as physiochemical effects, that may alter digoxin absorption. Our results indicate no significant differences in absorption as determined by C_{max}-C_{min} and t_{max} values, suggesting that simultaneous administration is unlikely to affect digoxin absorption. Furthermore, since we did not administer intravenous digoxin, the actual effect on digoxin bioavailability is unknown. Along this line, our results may also be explained if hawthorn blocked P-glycoprotein in the gut and at the same time reduced the amount of digoxin available for absorption through a physical or chemical interaction. It should also be emphasized that this only applies to digoxin, as it is not known whether haw-

thorn absorption is affected. While we did not measure hawthorn's individual components, we did use a standardized product made by a reputable manufacturer, making lack of hawthorn absorption highly unlikely.

Second, although no statistically significant pharmacokinetic interaction was observed, close inspection of the data suggests that hawthorn coadministration does result in a quantitatively small decrease in absorption and increase in the clearance of digoxin, presumably related to the mild induction of P-glycoprotein activity. This interpretation is based on the finding that AUC, C_{max}, C_{max}-C_{min}, and C_{min} were lower and renal clearance was higher in the digoxin plus hawthorn group. In fact, C_{min} was approximately 22% lower in this group, a difference that approached our a priori threshold level ($p \leq 0.05$) for statistical significance ($p = 0.054$). The reason that these more modest differences were not considered statistically significant is that the study was only adequately powered to detect differences of ≥ 25%. Even though our findings suggest that hawthorn causes mild induction (< 25% change) of P-glycoprotein activity, the clinical significance of this is anticipated to be minor in most patients. Certainly, the concern expressed in the clinical herbal medicine literature that hawthorn could increase the risk of digoxin toxicity is not supported by this study.

A third consideration is that the true half-life for many of the hawthorn constituents is unknown. In the absence of definitive pharmacokinetic studies of hawthorn, we assumed that 21 days would be sufficient time to reach hawthorn steady state. Whether a longer study period would yield significant results is unknown. It should be mentioned that the study time period for the St. John's wort study was 15 days and that other studies have shown alterations in P-glycoprotein activity (inhibition or induction) over a much shorter time period than 21 days.[11,17]

Finally, this study was done in normal subjects and used only one dosage of hawthorn. Whether differences would be seen in patients with heart failure, the likely setting for coadministration, or with higher hawthorn doses is unknown. However, the dosage investigated herein is identical to that being used in a large-scale clinical trial of hawthorn[6] and is similar to or higher than doses from numerous studies cited in a recent review of hawthorn pharmacology.[23]

In conclusion, coadministration of hawthorn with digoxin resulted in only modest changes in digoxin pharmacokinetics, differences that did not achieve statistical significance. We hypothesize that these differences are a result of mild P-glycoprotein induction likely due to the presence of quercetin and various quercetin glycosides in the hawthorn extract. In addition, there was no evidence of any pharmacodynamic interaction, as measured by ECG, heart rate, and blood pressure. In total, these findings suggest that both drugs may be given together safely in the clinical setting in the doses studied.

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